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Infectious Mononucleosis

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems (such as dizziness, pruritus, insomnia, shoulder pain and urinary tract infections) encountered in primary care practice that generally do not fall into well-defined subspecialty areas and are rarely discussed thoroughly in medical school, house staff training, textbooks and journals. Often the pathophysiology is poorly understood and clinical trials to assess the effectiveness of diagnostic tests or therapies may be lacking. Nevertheless, these problems confront practitioners with practical management questions.

The articles in this series discuss new tests and therapies and suggest reasonable approaches even when definitive studies are not available. Each article has several general references for suggested further reading. We hope this new series will be of interest and we welcome comments, criticisms and suggestions.

—BERNARD LO, MD
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Series' Editors

INFECTIOUS MONONUCLEOSIS (IM) is an acute febrile illness of late adolescence and early adulthood caused by the Epstein-Barr virus (EBV), a DNA virus of the herpesvirus group. EBV is ubiquitous and, by adulthood, 90 percent to 95 percent of people have demonstrable EBV antibodies. In the United States, half of children aged 5 have had EBV seroconversion and in many the infection is subclinical. A second peak of infection occurs in late adolescence.

IM is a disease of low infectivity. College roommates of patients with IM have no greater frequency of seroconversion than the general susceptible population. The disease is probably spread by intimate oral contact in young adults, but because there is such a high incidence of asymptomatic carriers, only 5 percent to 10 percent of patients with acute illness can give a history of exposure.

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Clinical Presentation

The typical patient with IM is a young adult aged 15 to 25. Most patients have a gradually worsening prodrome of malaise, headache, fatigability, chilliness, feverishness, anorexia, eyelid edema, and (if they are smokers) a dislike for cigarettes. The headache is retroorbital and there may be photophobia. Except for the presence of eyelid puffiness, these early symptoms are nonspecific and usually last several days. A characteristic clinical triad of fever, cervical adenopathy

and sore throat follows; this is observed in 80 percent to 90 percent of cases in young adult patients.

Fever is virtually always present, with the usual temperature range being between 38° and 39.5°C (100° and 103°F). In most cases of IM, the duration of the acute illness is equivalent to the duration of the fever, usually two to three weeks.

Cervical lymphadenopathy becomes prominent during the first week, stabilizes during the second week and then slowly remits, rarely lasting more than a month. Adenopathy of bilateral posterior cervical nodes is most characteristic, with axillary and inguinal adenopathy less common. Occipital nodes are usually normal, a helpful differential feature from rubella, and hilar adenopathy is very rare. The lymphadenopathy is bilateral and painless, and nodes are not red or fluctuant. There is no correlation between the size of the nodes and the duration of the illness.

Sore throat may be the most troublesome feature of IM. It usually begins during the first week and subsides after the second. On examination exudative pharyngitis may be mimicked. A recurrence of sore throat suggests superimposed streptococcal infection. Transient *palatal petechiae* at the junction of the hard and soft palates are noted in a third of patients, typically during the second week.

Splenomegaly is present in about half of patients, often associated with tenderness to palpation. Vigorous repeated palpation should be avoided to prevent splenic rupture. The splenomegaly usually follows the pattern of change in lymph nodes, returning to normal by one month. However, splenomegaly may be persistent for up to six months or, rarely, for years. Hepatomegaly, which is usually asymptomatic, is seen in 10 percent of patients, but more common is first-percussion tenderness over the liver. *Jaundice* is seen in 5 percent of cases and generally has a benign course. Infrequently, hepatitis can be the predominant presentation and is apt to be associated with high fever, unlike other viral hepatitides.

In upwards of 80 percent of patients with IM a *rash* develops when they are given ampicillin, with a nonpruritic macular or macular-papular rash occasionally developing spontaneously. The former does not imply permanent hypersensitivity to ampicillin, nor is it specific for IM, since it can complicate cytomegalovirus (CMV) infection.

Nasal stuffiness, cough, sputum production, chest pain, joint pains, painful lymph nodes, diarrhea, dysuria or severe abdominal pain are not found.

Because IM is a disease mainly of young adults, most patients over 40 have had previous exposure to EBV and are immune to reinfection. Rarely, IM may develop in older patients lacking such immunity. Difficulty in making the diagnosis stems from not considering the disease in this age group, and older patients may have less cervical adenopathy. Serologic studies do not differ from those of infected young adults, but the clinical course may be severe and complicated.

Laboratory Features

The pertinent laboratory abnormalities in IM are hematologic, serologic and hepatic. In the usual clinical presentation, IM can be diagnosed with a heterophil test and complete blood count only.

The hematologic criterion for diagnosis is an increase in mononuclear cells of greater than 50 percent, with the occurrence of at least 10 percent atypical lymphocytes. During the second and third weeks, the elevated lymphocyte count peaks at 12,000 to 20,000 and occasionally may reach 50,000 per cu mm. Some patients have a leukopenia early in the illness.

Mild neutropenia (2,000 to 3,000 per cu mm) and thrombocytopenia (100,000 to 140,000 per cu mm) are common and resolve in a month. The hemoglobin is usually normal, a helpful differentiating feature from lymphoma and leukemia.

The serologic basis for the diagnosis of IM is a positive heterophil test; the Monospot Slide Test for Infectious Mononucleosis (Ortho Diagnostic Systems, Inc., Raritan, N.J.) is one of numerous available rapid tests for heterophil antibodies. If the Monospot test is negative but it is clinically indicated, one should retest in seven to ten days. Approximately 40 percent of patients have a positive test during the first week, increasing to 80 percent by the third week. In 20 percent, the Monospot test continues to be positive a year after the onset of the illness. The Monospot test should never be considered diagnostic in the absence of clinical or hematologic features of IM. Unusual false-positive results on Monospot tests occur in cases of other viral illnesses (especially rubella) or serum sickness and in patients with non-Burkitt's lymphoma with unrelated EBV infection. In a person with persistently negative Monospot findings in whom serologic confirmation of

IM is necessary, one may do a differential heterophil absorption test, or tests specific for EBV antibodies. The lack of any EBV antibodies rules out the disease.

Because liver function is almost always abnormal in IM, this need not be checked in a routine case. Serum transaminases are most commonly elevated to two to three times normal, with mild elevations of serum alkaline phosphatase and serum bilirubin. The changes are greatest during the second week, with gradual decline over the next month.

In rare cases in which hepatitis predominates in the clinical presentation, the enzymes differ from those of hepatitis A or B. There is a dissociation in IM between an elevated serum alkaline phosphatase and a low serum bilirubin, with moderate rises in serum transaminases.

Complications

IM is usually a benign, self-limited illness and complications are rare, occurring in less than 1 percent of patients. Despite the brevity of the acute illness, debility and lethargy may last for two to three months.

Splenic rupture is a life-threatening complication and occurs in 0.2 percent of cases. As abdominal pain is distinctly unusual in IM, its presence should alert a physician to the possibility of splenic rupture. It is a misconception that IM may mimic acute appendicitis from mesenteric adenitis. Splenic rupture can occur spontaneously, as well as after abdominal trauma. Syncope in a patient with IM should bring to mind splenic rupture, and as long as the spleen is enlarged, the risk of rupture persists.

Neurologic complications are rare but aseptic meningitis, meningoencephalitis and peripheral neuropathies have been reported.

Airway obstruction from massively enlarged tonsils and pharyngeal edema may occur. *Pneumonitis* is seen on chest x-ray films in 2 percent to 5 percent of patients and *pleural effusions* are noted.

Severe *thrombocytopenia* due to increased platelet destruction can occur. *Anemia* is rare and, when present, the cause is hemolysis due to cold agglutinins directed against red cell antigen i. The direct Coombs' test may be positive.

Cardiac complications with nonspecific electrocardiographic changes, pericarditis and myocarditis can occur.

Differential Diagnosis

If patients with the clinical triad of lymphadenopathy, fever and sore throat have atypical lymphocytes and a positive heterophil test, the diagnosis of EBV mononucleosis is established. Difficulties arise when typical clinical features of IM are observed with repeatedly negative heterophil tests, more common in the pediatric population. Most of these patients have significant antibody titers to EBV, suggesting that the disease is still due to the virus. Other causes of heterophil-negative mononucleosis are CMV and toxoplasmosis. CMV follows transfusions more frequently than does EBV, and sore throat is not a major feature. Viral hepatitis may present with low-grade fever and lymphadenopathy, but is also not accompanied by pharyngitis. Streptococcal sore throat may be confused with IM. Here, lymphadenopathy is anterior cervical and splenomegaly is absent; in some cases, the two diseases coexist. Drug-induced hypersensitivity reactions, particularly the lymphadenopathy associated with recent institution of phenytoin, may be excluded by the history.

The most worrisome differential diagnosis is lymphoma or leukemia. Anemia is more common in the malignant disorders. Hyperuricemia should not be used as a laboratory test to differentiate between lymphoma and IM, as it can be seen in the acute phase of mononucleosis.

Treatment

The treatment of IM is mainly supportive because more than 95 percent of patients recover uneventfully without specific therapy. Isolation is unnecessary and during the acute phase of the illness, bed rest is encouraged though patients' symptoms govern the degree of activity. Gradual increase in activity beginning a week after a patient becomes afebrile and spanning a three- to four-week period is prudent, but vigorous activity should be avoided for three to six months to prevent splenic rupture. Patients should be advised to contact their physician immediately if abdominal pain develops.

Aspirin or acetaminophen is helpful for the control of fever and headache, and saline or lidocaine gargles relieve the sore throat. There is no indication for the routine use of antibiotics in IM. If their use becomes necessary due to a concomitant streptococcal pharyngitis, administration of ampicillin should be avoided because of the high incidence of rash.

Corticosteroid therapy should be reserved for

severe manifestations or complications of the disease, such as impending airway obstruction, hemolytic anemia, severe thrombocytopenia, considerable neurologic involvement and myocarditis. Prednisone in dosages of 60 to 80 mg a day is given. Because the response is usually rapid, the dosage may be tapered over one to two weeks.

Transfusions are seldom necessary in uncomplicated IM. If required they should be given at 37°C because a patient with anemia nearly always has cold agglutinins.

Finally, because the EBV can be cultured for several months from a patient's lymphocytes, blood donation should be postponed for at least six months after the onset of the illness.

GENERAL REFERENCES

Chervenick PA: Infectious mononucleosis. DM December 1974, pp 1-29

Evans A: Chap 107, *In* Williams W (Ed): Infectious Mononucleosis in Hematology, 2nd Ed. New York, McGraw-Hill, 1977, pp 956-968

Fiala M, Heiner DC, Turner JA, et al: Infectious mononucleosis and mononucleosis syndromes—Clinical virological and immunological features (Medical Progress). West J Med 1977 Jun; 126:445-459

Horwitz CA: Practical approach to diagnosis of infectious mononucleosis. Postgrad Med 1979 Jun; 65:179-184

Schooley R, Dolin R: Epstein-Barr virus (infectious mononucleosis), chap 119, *In* Mandel G (Ed): Principles and Practice of Infectious Diseases. New York, Wiley Medical Publications, 1979; pp 1324-1341

Fifth National Impaired Physician Conference

PHYSICIAN IMPAIRMENT and its effect on patients, families and colleagues is the subject of the American Medical Association's Fifth National Conference on the Impaired Physician, to be held September 22 through 25, 1982, in Portland, Oregon. The meeting is cosponsored by the Oregon Medical Association and the Multnomah County Medical Society and will be held at the Portland Marriott.